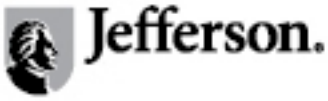

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Remote preoperative tonic-clonic seizures do not influence outcome after surgery for temporal lobe epilepsy.

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Title: Remote preoperative tonic-clonic seizures do not influence outcome after surgery for temporal lobe epilepsy.

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Abstract

Objectives: Tonic-clonic seizures are associated with greater chance of seizure relapse after anterior temporal lobectomy. We investigated whether the interval between the last preoperative tonic-clonic seizure and surgery relates to seizure outcome in patients with drug-resistant mesial temporal lobe epilepsy (MTLE).

Methods: In this retrospective study, patients were prospectively registered in a database from 1986 through 2014. Postsurgical outcome was categorized as seizure freedom or relapse. The relationship between surgical outcome and the interval between the last preoperative tonic-clonic seizure and surgery was investigated.

Results: One-hundred seventy-one patients were studied. Seventy nine (46.2%) patients experienced tonic-clonic seizures before surgery. Receiver operating characteristic curve of timing of the last preoperative tonic-clonic seizure was a moderate indicator to anticipate surgery failure (area under the curve: 0.657, significance; 0.016). The best cutoff that maximizes sensitivity and specificity was 27 months; with a sensitivity of 0.76 and specificity of 0.60. Cox-Mantel analysis confirmed that the chance of becoming free of seizures after surgery in patients with no or remote history of preoperative tonic-clonic seizures was significantly higher compared with patients with a recent history (i.e., in 27 months before surgery) ($p = 0.0001$).

Conclusions: The more remote the occurrence of preoperative tonic-clonic seizures, the better the postsurgical seizure outcome, with at least a two year gap being more favorable. A recent history of tonic-clonic seizures in a patient with MTLE may reflect more widespread epileptogenicity extending beyond the borders of mesial temporal structures.

Introduction

Temporal lobe epilepsy (TLE) associated with mesial temporal sclerosis (MTS) is one of the most common types of drug-resistant epilepsy referred for surgery [1, 2]. The potential efficacy of resective surgery in patients with drug resistant MTS-TLE is undisputed. However, there are still uncertainties about which patients will benefit most [3-6]. One of the most consistent risk factors associated with poor outcome after surgery for drug-resistant TLE in the literature is a history of preoperative tonic-clonic seizures [6-9]. However, no investigators have defined what is meant by the presence of tonic-clonic seizures. It is not clear whether this refers to ongoing recent seizures or more remote seizures, or both. Besides, how the term "remote" should be defined is unknown. In this study, we evaluated a large surgical cohort, examining seizure outcome during postsurgical follow-up in patients with drug resistant MTS-TLE. The significance of the latency from the last preoperative tonic-clonic seizure to surgery with respect to the outcome after surgery was investigated.

Material and methods

In this retrospective study, all patients with a clinical diagnosis of drug-resistant TLE due to MTS, who underwent epilepsy surgery at the Jefferson Comprehensive Epilepsy Center and had a minimum of one year postoperative follow-up, were assessed. Patients were prospectively registered in a database from 1986 till 2014. Historical data was obtained by board certified neurologists. There was no age limit to enter the study. All patients underwent a comprehensive presurgical evaluation [10]. Magnetic resonance imaging (MRI) studies were analyzed by neuroradiologists, neurologists, and neurosurgeons with expertise in epilepsy. We classified patients as having MTS if they had clear signs of mesial temporal atrophy and/or sclerosis in

their brain MRI. Patients with dual pathology and also patients with incomplete data with regard to pre- and postoperative seizure information were excluded. Timing of the last preoperative tonic-clonic seizure was identified. To obtain the most accurate data, we reviewed the medical records of all patients in addition to our database query.

All patients had an anterior temporal lobectomy (ATL) including resection of mesial temporal limbic structures. They were followed for up to five years after surgery. Postsurgical outcome during the follow-up was classified into two groups; with sustained seizure freedom or relapsed (one or more seizures after surgery). Aura was not considered as a relapse; only postoperative tonic-clonic seizures and complex partial seizures were considered as relapse.

Age, gender, epilepsy risk factors (e.g., history of febrile seizures in childhood, family history of epilepsy, etc.), age at seizure onset (i.e., the first afebrile habitual seizure), seizure type(s) and history, date of surgery, date of the first relapse (if any) and date of the last contact with all patients were registered routinely.

Demographic variables and relevant clinical variables were summarized descriptively to characterize the study population. Timing of the last preoperative tonic-clonic seizure was compared between seizure free patients and those who had recurrence. Statistical analyses were performed using Pearson Chi-square, Fisher's exact, Mann-Whitney, and Kolmogorov-Smirnov tests. Time to event analysis was used to produce a Kaplan-Meier estimate of seizure recurrence. Cox-Mantel test was used to study annual rate of occurrence of first seizure after resective epilepsy surgery. Receiver operating characteristic curve was performed to identify the best cutoff point (maximum sensitivity + specificity) and the discriminatory ability of preoperative tonic-clonic seizures to correctly pick up all patients who had postoperative seizure recurrence. A

p-value less than 0.05 was considered as significant. This study was conducted with the approval by Thomas Jefferson University Institutional Review Board.

Results

From 1986 until 2014, 789 patients had anterior temporal lobectomy at our center; 770 patients had at least one year of follow-up. Of these, 309 patients had MTS in their MRI, 251 patients had other abnormalities (e.g., tumor, gliosis, vascular lesion, etc.) in their MRIs, 168 patients had a normal MRI, 19 patients had dual pathology and MRI was not available in 23 patients. Among patients with MTS, 171 patients (77 males and 94 females) had MTS-TLE with at least one year of postoperative follow-up and complete seizure data and most importantly, the timing of their last preoperative tonic-clonic seizure in our database and electronic medical record system. Ninety-two (53.8%) patients did not report any preoperative tonic-clonic seizures, but 79 (46.2%) persons experienced one or more tonic-clonic seizures before their surgery. Duration of epilepsy before surgery was similar in these two groups (Table 1). Demographic and clinical characteristics of these two groups are shown in Table 1. Ninety-one (53.2%) patients were seizure free and 80 (46.8%) persons experienced one or more seizures after surgery. Receiver operating characteristic (ROC) curve of timing of the last preoperative tonic-clonic seizure was a moderate indicator to anticipate surgery failure (i.e., seizure recurrence) (area under the curve: 0.657, standard error: 0.063, significance; 0.016, 95% confidence interval: 0.534-0.781) (Figure 1). The best cutoff point was at 27 months. At this time, the sensitivity was 0.76 and the specificity was 0.60. We then followed up with a Kaplan-Meier curve using the cutoff for preoperative TCS developed from the ROC curve, and confirmed a striking difference in outcomes between recent and distant preoperative TCS. Cox-Mantel analysis confirmed that, the

chance of becoming free of seizures after surgery in patients with no history of preoperative tonic-clonic seizures (92 patients) or those with a remote history of this seizure type (32 patients) was significantly higher compared with patients with a recent history of any preoperative tonic-clonic seizures (47 patients) (i.e., in 27 months before surgery) ($p = 0.0001$) (Figure 2). Frequency of preoperative TCSs in patients with a remote history of such seizures was 0.13 ± 0.47 per month and in those with a recent history of TCS was 0.84 ± 1.71 ($p = 0.02$). Frequency of preoperative complex partial seizures in patients with a remote history of TCSs was 5.2 ± 7.2 per month and in those with a recent history of TCS was 8.9 ± 14.2 ($p = 0.1$).

Discussion

Tonic-clonic seizures have been observed as a risk factor for seizure recurrence after ATL for drug-resistant MTS-TLE [6]. In one previous study of 116 consecutive patients who had temporal lobe surgery for drug-resistant epilepsy and MTS [9], the occurrence of generalized tonic-clonic seizures was significantly associated with a poor outcome. In another study of 280 patients who underwent TLE surgery [7], patients with a history of generalized tonic-clonic seizure(s) were significantly less likely to remain seizure free (odds ratio 0.47, 95% CI 0.25–0.90, $p = 0.02$). Another study of 339 patients followed for more than two years found that absence of generalized tonic-clonic seizures and presence of hippocampal atrophy on MRI were significantly associated with remission in patients with medial temporal resection [11]. These findings are consistent, but none clearly defines whether remote tonic-clonic seizures were relevant in the analyses and how they should be considered and defined. The major finding of the current study is that the timing of the last preoperative tonic-clonic seizure correlates with

postsurgical seizure outcome, so that for the purpose of determining surgical prognosis, remote tonic-clonic seizures (i.e., seizures more remote than 27 months before surgery) do not count. Why might this be? Ongoing or recent or more frequent tonic-clonic seizures in a patient with MTS may reflect more widespread epileptogenicity extending beyond the borders of mesial temporal structures. Evidence obtained with fMRI suggests more widespread derangements in brain function and connectivity in TLE patients with tonic-clonic seizures (compared with those without these seizure type) [12]. Lack of tonic-clonic seizure might also indicate a greater preservation or upregulation of inhibitory mechanisms that serve to prevent more extensive spread of ictal discharges to diencephalic and brainstem structures necessary for tonic-clonic seizures [13]. Further investigation of underlying physiology and anatomy is warranted to better define the mechanisms for this process.

Our study has some limitations. Patients in the study had different follow up times after surgery. Ideally, all patients would have a consistent follow up time, in which case the outcome is simply whether or not a seizure occurred in that interval. Our data does not fit that model. For the purposes of our ROC curve analysis, patients were classified as either having had a postoperative seizure or not, during the available follow up time, which differed between patients. Since most seizures occurred within the first year of follow up (Figure 2), and the average follow up is over 4 years (Table 1), it seems unlikely to have missed substantial numbers of individuals likely to relapse. For preoperative TCS, similar issues arise. The duration of epilepsy was, however, similar in those who did and did not have preoperative TCS (Table 1). Aura was not considered as a relapse; only postoperative tonic-clonic seizures and complex partial seizures were considered as relapse in our study. However, in some jurisdictions auras prevent driving, hence an 'auras only' postoperative outcome is less favorable in terms of daily function than complete

seizure freedom. Therefore, the data in this paper is not completely applicable in those jurisdictions. Finally, many patients (138 patients out of 309 patients; 45%) from our database were excluded from this study due to incomplete seizure data and most importantly, unavailability of the data on the timing of their last preoperative tonic-clonic seizure. This may induce bias.

Conclusions

We evaluated a large surgical cohort, examining seizure outcome during a long-term postsurgical follow-up in patients with MTS-TLE who had undergone epilepsy surgery for drug-resistant seizures. We observed that the timing of the last preoperative tonic-clonic seizure correlates with postsurgical seizure outcome. While a gradual improvement in outcome was noted as tonic-clonic seizures became more remote, it appears that one can use a cutoff point of 27 months to predict seizure outcome. Hence, we can refine published observations [6-9] regarding the prognostic significance of preoperative tonic-clonic seizures. The preoperative tonic-clonic seizures do matter, but the more they recede into the distance the less relevant they become.

Disclosures

Ali A. Asadi-Pooya, M.D., consultant: Cerebral Therapeutics, LLC and UCB Pharma. Amin Rabiei, M.D. and Edward J. Gracely, Ph.D., report no disclosures. Michael R. Sperling, M.D., Consulting: Medtronics through Thomas Jefferson University; Research: contracts with Thomas Jefferson University: Eisai, UCB Pharma, Sunovion, SK Life Sciences, Marinus, Lundbeck, Neurelis, Medtronics, Accorda, Upsher-Smith, Brain Sentinel, Pfizer. Michael R. Sperling, M.D. is an editor-in-chief of Epilepsia.

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Figure 1. Receiver operating characteristic curve (ROC curve) of timing of the last preoperative tonic-clonic seizure as a prognostic factor for surgery outcome in patients with drug-resistant MTS-TLE.

Figure 1 legend. Receiver operating characteristic curve (ROC curve) of timing of the last preoperative tonic-clonic seizure was a moderate indicator to anticipate surgery failure (i.e., seizure recurrence); Arrow indicates optimal cutoff point. MTS-TLE: Mesial temporal sclerosis-Temporal lobe epilepsy.

Figure 2. Kaplan-Meier graph showing pattern of occurrence of the first seizure after resective epilepsy surgery in patients with MTS-TLE, by preoperative tonic-clonic seizure groups.

Figure 2 legend. The chance of becoming free of seizures after surgery in patients with no history of preoperative tonic-clonic seizures or those with a remote history of this seizure type was significantly higher compared with patients with a recent history of any preoperative tonic-clonic seizures. Remote history of TCSs (not in 27 months preceding surgery); Recent history of TCSs (in 27 months preceding surgery). Vertical bars indicate censored observations. TCS: tonic-clonic seizure; MTS-TLE: Mesial temporal sclerosis-Temporal lobe epilepsy.